REMARKS

I. The Subject Matter of the Claims

The subject matter of the claims relates, in general, to methods of stimulating stromal cell growth using compositions comprising stem cell factor (SCF).

II. Application Formalities

The Examiner indicates that the application does not comply with the sequence listing rules, specifically claims 72-74 recite a figure number rather than a sequence identifier. The claims have been amended to include sequence identifiers, thereby obviating the rejection.

III. Support for the Amendment to the Claims

The claims have been amended to remove reference to figure numbers (claims 72-74) and to clarify claim terminology (claims 78 and 80). The amendment to claim 73 to remove particular polypeptide fragments has been made to expedite prosecution and not for reasons related to patentability. The amendment to the claims include no new matter.

IV. Objections to the Specification

The Examiner objects to the specification for recitation of a patent application without having updated information, for example in the first paragraph and in the text. Applicant has amended the first paragraph and those paragraphs in the specification as needed.

The Examiner indicates that the Brief Description of the Drawings does not refer to all the drawings, e.g., Figures 24A-B, 29A-B, 30A-B, 42A-D, 44A-C and 56A-B. The respective paragraphs in the specification have been amended to reflect these drawings.

V. Patentability

A. The Rejection of Claim 71-85 Under 35 U.S.C. §112, First Paragraph, Enablement, Should Properly Be Withdrawn

The Examiner rejects claims 71-90 as not enabled asserting that the application does not demonstrate to one of ordinary skill in the art how to perform the method of the invention using stromal cells. The Examiner contends that the application does not teach one of ordinary skill how to administer SCF to stimulate stromal cells and that delivery of protein therapeutics is unpredictable. Further, the Examiner contends that the application does not teach which of the SCF polypeptides would be effective, causing undue burden on a person having ordinary skill to determine the SCF composition. Applicants respectfully disagree.

As acknowledged by the Examiner, the specification teaches SCF stimulation of bone marrow-derived cells in vitro and administration of SCF to mice and primates in vivo. For example, pages 172-173 of the specification describe that 10 ng/ml to 100 ng/ml of purified SCF stimulates bone marrow cell growth in vitro, while pages 106-109 teach administration of 30, 100, or 200 μg/kg/day of SCF to Steel mice or primates. These teachings describe dosages that stimulate cells in vitro which result in measurable cell growth. Also noted by the Examiner, the specification teaches that stromal cells expressing SCF stimulate growth of hematopoietic cells (page 177, lines 14-22).

However, contrary to the Examiner's assertion, the art does teach that stromal cells are capable of stimulation by SCF. Parrott et al (*Endocrinology* 138:3819-27, 1997, submitted herewith) teaches that SCF stimulates ovarian theca cells, which are considered stromal cells of the reproductive system. These cells are important in development of the female reproductive tract, which the specification teaches is one of several non-hematopoeitic activities in which SCF plays a role (page 28, lines 3-14). Krieger et al., (*Eur J Haematol.* 54:262-9, 1995, submitted

herewith) disclosed that stromal cells isolated from patients with aplastic anemia expressed only low levels of soluble SCF, and that addition of exogenous SCF to the cell culture resulted in growth of the bone marrow stromal cells. Additionally, Simak et al., (*Histol Histopathol.* 15:365-74, 2000, abstract included) indicate that both SCF and c-Kit transcripts were present in cultured epithelial cells of benign prostatic hyperplasia (BPH) isolates, and in cultures of stroma cells from both normal and BPH.. These references indicate that a worker of ordinary skill can readily isolate stromal cells from stem cells or other cells in culture, and readily assess the effects of SCF on this stromal cell population.

Further, a worker of ordinary skill in the art would reasonably expect that the amounts of SCF used to stimulate bone marrow growth as taught in the specification would be similar to amounts necessary to stimulate growth of stromal cells. This is indeed the case. See Parrot et al., *supra*, which discloses use of 10–50 ng/ml SCF to stimulate theca cell growth. The SCF concentrations used in Parrott et al. to stimulate stromal cells are similar to the effective amount of SCF disclosed in the specification to stimulate bone marrow cells. Thus, both the teachings in the specification and the art show that SCF polypeptides bind to and stimulate its receptor on a multiplicity of cell types, including stromal cells, within relatively the same concentration ranges.

In addition, the specification teaches that administration of SCF presents no adverse reactions in therapeutic use of SCF (page 108, lines 33-34). The same is shown to be true with administration of several different isoforms of SCF (page 109, lines 7-16). These results demonstrate that the administration of SCF is predictable.

Further, the specification discloses at page 185 that SCF polypeptides recited in the claims are effective at stimulating growth and proliferation of bone marrow cells. C-kit is the

only receptor identified for SCF, and therefore the SCF receptor on the surface of bone marrow cells and stromal cells is the same. This result indicates that any SCF polypeptide analog or isoform binds to the SCF receptor on the cell surface and activates the receptor. Moreover, Lev et al., (*J Biol Chem* 267:10866-73, 1992, submitted herewith) showed that CHO cells transfected with SCF receptor were bound and activated by SCF as measured by tyrosine phosphorylation. Thus, a worker of ordinary skill in the art taught that an SCF polypeptide stimulates bone marrow cells through the SCF receptor would reasonably expect that the same SCF polypeptide would bind to the same SCF receptor on a stromal cell, thereby stimulating said stromal cells.

A worker of ordinary skill can readily take any SCF fragment and assess its activity against a bone marrow cell as in Example 9, or substitute any stromal cell, such as an ovarian stromal cell or bone marrow stromal cell, in the assay. This routine experimentation does not present an undue burden to a person of ordinary skill. Additionally, because the SCF polypeptide is well characterized in the specification, including the full sequence, location of Cys residues and the transmembrane domain (see page 184, lines 17-29), a worker of ordinary skill would not have to determine the structure of the SCF polypeptides. As such, there is no undue burden on the person of ordinary skill to determine if an SCF polypeptide binds to and activates the SCF receptor on a stromal cell.

Given the teachings in the specification of how to administer SCF in order to stimulate cells, the teachings that administration of different isoforms of SCF are safe, effective and predictable, and the demonstration that SCF that binds to and stimulates the same receptor on an stromal cell or bone marrow cell, the specification teaches one of ordinary skill in the art how to make and use an SCF polypeptide to stimulate epithelial cells without undue burden to a worker of ordinary skill.

For these reasons, the rejection of the claims 71-90 under 35 USC §112, first paragraph, as assertedly not enabled should properly be withdrawn.

B. The Rejection of Claims 78 and 80 Under 35 U.S.C. §112, Second Paragraph, Should Properly Be Withdrawn

The Examiner rejects claims 78 and 80 as indefinite asserting that acronyms in the claims, e.g., IL-1 or G-CSF, are indefinite. The claims have been amended for clarification, thereby obviating the rejection.

VI. Conclusion

No fees are believed due in connection with this paper. However, if additional fees are deemed necessary, the Commissioner is hereby authorized to charge Marshall, Gerstein and Borun deposit account number 13-2855.

Applicants submit that the application is now in condition for allowance and respectfully request notice of the same.

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Respectfully submitted,

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